Cell Stem Cell

Editors' Notes

Testing Testis

Understanding the molecular pathways that regulate male germ stem cell proliferation and differentiation will contribute to research efforts related to fertility and testicular cancer. In their Research Article, Shinohara and coauthors have used genetic manipulations to mimic specific signal cascade activation in spermatogonial stem cells (SSCs) independently of their normal requirements for growth factors in culture. Their results reveal that the Ras-cyclin D2 pathway mediates the balance between SSC renewal and differentiation and upon excessive activation can lead to hallmarks of testicular germ cell tumors. In addition to functioning as unipotent germ stem cells, SSCs exhibit the potential to dedifferentiate in culture and regain functional pluripotent status, as also illustrated in this issue. In their Resource article, Schöler and colleagues describe a consistent method for isolating spontaneously arising cell lines from purified populations of SSCs. These clonal lines are capable of contributing to germline-competent chimeric mice, thus demonstrating their true pluripotency, and improving upon previous efforts that described rare testis-derived populations with ESC-like or EpiSC-like functional traits.

Consider the Source

As the range of sources of pluripotent cells increases, ethical conversations will turn to focus on which cells or derivatives can, or should, be used clinically and/or for research. In their Forum article, Mathews and colleagues encourage the development of regulations to oversee pluripotent cell-derived gamete production, even in advance of achieving this lofty scientific goal. Similarly, in the ISSCR pages of this issue, the Ethics Committee reports their recommendations about when it is appropriate to pursue interspecies SCNT for the derivation of hESCs, also in the absence of evidence that such a feat can be accomplished in a repeated, feasible manner. It is currently not possible to test whether hESC lines developed after SCNT into a nonhuman oocyte would be comparable to those derived without crossing an interspecies barrier. However, in this issue, Lowry and colleagues present some of the best evidence to date that pluripotent cells derived by different means may indeed be best considered distinct. In their Resource article, the authors compare human and mouse ESCs and iPSCs and find that the somatic-derived pluripotent cells exhibit distinct epigenetic and miRNA expression profiles, even if no genetic alterations from the reprogramming process remain. The cells do nevertheless show strong similarities too, and in a separate Resource article, Cheng and coauthors demonstrate that efficient genetic modification of both ESCs and iPSCs can be accomplished using zinc finger (ZFN) technology. As our understanding progresses, it seems likely that selection of one pluripotent cell source over another will depend on the properties of the cells and the specific application being pursued.

Intersecting Platforms

Biological research has always been interdisciplinary, but recent years have seen a greater push for collaboration across distinct platforms. In their Review article, Guilak and colleagues highlight several bioengineering perspectives for the *CSC* audience. They discuss, among other things, how studies of extrinsic forces have been applied to promote and direct the expansion or differentiation of various stem cell populations, including ESCs and mesenchymal stem or multipotent stromal cells (MSCs). MSCs themselves in fact also provide an example of "interdisciplinary" activity through evidence that they function as immune modulators in animal models. In their Research Article, Prockop and colleagues reveal that MSCs mediate improvement in an experimental model of cardiac infarction by secreting TSG-6, an anti-inflammatory molecule. By either blocking MSC production of TSG-6 or providing the protein in recombinant form, the authors demonstrate that at least some of the clinical potential of MSCs may derive from their secretion of soluble mediators, rather than long-term cellular engraftment.

Translating Leukemia

Many mouse models of human leukemias exist, but the wide range of oncogenes and promoters used and the varied initiating populations make it difficult to compare results across systems. In this issue, Hock and colleagues generate an inducible *TEL-AML1* construct driven by the *TEL* promoter and trigger oncogene expression in multiple populations, over several developmental stages. Their analysis reveals that the translocation responsible for the most common childhood leukemia leads to a preleukemic state, including expansion of the HSC population and an early block in lymphocyte development. However, transformation to yield fatal disease requires additional mutagenic hits, and furthermore, this process depends on targeting the translocation to the primitive pool of blood progenitors, as opposed to more differentiated progeny. Moving closer to the clinic, in their Research Article, Lock and coauthors present a potential therapeutic paradigm for AML, using mice as xenogenic hosts for primary AML biopsies. They demonstrate that neutralizing the IL-3 receptor α chain with anti-CD123 antibodies reduced the survival of a cell population containing isolated leukemic stem cells, lowered the leukemic burden in recipient mice, and impaired the transfer of disease in secondary hosts. Both approaches to teasing apart the origin and behavior of human leukemia, while distinct, demonstrate how the field continues to fine-tune approaches to preclinical assessment of potential therapeutics.